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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Fengqi Ye

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RABIN & Berdo, PC

1101 14TH STREET, NW

SUITE 500

WASHINGTON, DC 20005

EXAMINER

BERCH, MARK L

ART UNIT

PAPER NUMBER

1624

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/580,561	Applicant(s) YE ET AL.	
	Examiner /Mark L. Berch/	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 10 is/are allowed.
- 6) ☒ Claim(s) 1-8, 11-13 and 15 is/are rejected.
- 7) ☒ Claim(s) 9, 14 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Claims Construction

The “composed by connecting” language as set forth below is unclear and probably incorrect. Accordingly, the claims are treated as if these are product by process claims, so that “composed by connecting” is read as “prepared by reacting” for examination purposes.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 11-13, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The “composed by connecting” language is unclear and probably incorrect. If these two were “connected”, then the e.g. halo would still have to be present, and where the connection occurs would be vague. Applicants may wish to replace “composed by connecting” with “prepared by reacting” for proper product by process claims, or use a structural formula as has been done in claim 9.
2. Semi-synthetic is unclear. How does this differ from “synthetic”?
3. The “salts thereof” both in claim 1 and dependent claims is unclear. Is the salt the salt of the starting material or the final product?
4. The claim 2 term “organic alkali salt” is unclear. Which word applies? Judging from the wording of claim 3, the word “alkali” needs to be removed.

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5. Claims 11 and 15 provide for the use of the esters, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 11 and 15 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4, 5-9, 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baltzer or English, these in view of Okonogi, 6150350, Crosby, Bauernfeind, Aubert, Xiong(1995), Fu, Xiong(2004).

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Baltzer teaches the concept of a mutual prodrug of β -lactam antibiotics and β -lactamase inhibitors; see title. These were formed in the exact same way applicants do, by esterifying both the β -lactam antibiotic and β -lactamase inhibitor to the same methylene group. The advantage of doing this over the alternative, a mixture of the two compounds, is set forth in the paragraph bridging pages 1183-1184, viz., that “both the antibiotic and the inhibitor are present simultaneously in appropriate balance at the site of the infection. This will not usually be the case when the two compounds are given as a combination because each drug in a combination will have its own individual profile with respect to rate of absorption, distribution and duration of action.” This established that one of ordinary skill in the art would be well motivated to prepare the mutual prodrug rather than the combination of β -lactam antibiotic and β -lactamase inhibitor.

English has a very similar teaching. Again, sulbactam is linked in the same way to a penicillin. Page 346 notes the advantage to be expected: “There are several advantages inherent to carboxyl-terminated double-ester prodrugs for oral delivery of pharmaceutical agents. The carboxyl moiety imparts improved water solubility, especially as the pH rises, as in transit from the stomach to the small intestine. It also provides improved prospects for isolation of crystalline solids as free acids or as sodium salts, thus creating options to improve formulation of oral delivery forms. Another advantage is the formation of potentially innocuous organic diacids as by products after hydrolysis to the parent drug in vivo. Clinically, these advantages can be translated to drugs that are more efficacious, safe, and convenient to use. In summary, the acid-termination concept of ester prodrug design has provided novel and effective delivery forms for the β -lactamase inhibitor sulbactam. Similar application to other drugs in order to improve oral bioavailability, formulation,

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water solubility, and simultaneous byproduct formation is suggested." The "Similar application to other drugs" would render such an approach obvious to any other drug which was already known to be synergistic with sulbactam.

The two examples of the primary reference, compounds 3 and 4, both employ sulbactam as the β -lactamase inhibitor. The β -lactam antibiotic in both cases is a penicillin. However, it would be obvious to use any " β -lactam antibiotic", as that is what the reference Baltzer teaches; again, see title and above cited paragraph. Likewise, English teaches "other drugs".

Okonogi, Table 4, teaches that sulbactam is an effective β -lactamase inhibitor when used with the cephalosporin cefotiam. Therefore, it would be obvious to prepare this mutual prodrug with cefotiam.

6150350 teaches synergistic combinations of other cephalosporins, and sulbactam. See patent claim 2. The organic salt is seen in the zwitterions of e.g. example 5, 9, etc.

The Crosby reference establishes that sulbactam is an effective synergist for the cephalosporin antibiotic cefoperazone, and indeed, this combination is sold commercially under the names of Cebanex, Zosul IM/IV, Cefocef, Sulperazon® (the sodium salt), Cefina-SB and other names.

Bauernfeind teaches synergist effect of sulbactam with Cefotaxime.

Aubert et al teaches synergist effect of sulbactam with ceftazidime, Cefpirome and cefepime for four strains; see page 158, last paragraph and figure.

Xiong(1995) also teaches synergist effect of sulbactam with ceftazidime, as the results state that sulbactam with ceftazidime was more effective against *P. aeruginosa* than ceftazidime alone.

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In Fu, it is seen that sulbactam is synergistic with cefsulodin in 30 of 32 strains of *Bacteroides*.

In Xiong(2004), note Table 2, which shows strong synergism between sulbactam and Cephalothin, Cefuroxime, Cefpodoxime, Cefotaxime, Ceftazidime and Ceftriaxone. Note that cefuroxime is named in claim 4, and 13 and is the second species in claims 9 and 14 and hence is applicable to those claims.

With regard to claim 3, it will not matter what salt is used for either of the starting materials, as the product remains an ester. Likewise which halo is the leaving group for claim 5.

Claim Objections

Claim 9 and 14 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 9 and 14 must end in a period.

Specification

Chinese characters must be removed from all tables; see e.g. top of page 9. The “acetdimethylamide” of example 9 and other examples is clearly wrong.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to /Mark L. Berch/ whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark L. Berch/
Primary Examiner
Art Unit 1624

9/18/2008